General

Guideline Title

Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease.

Bibliographic Source(s)

National Clinical Guideline Centre. Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Jul. 50 p. (Clinical guideline; no. 181).

Guideline Status

This is the current release of the guideline.

This guideline updates previous versions:

National Collaborating Centre for Primary Care. Lipid modification. Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. London (UK): National Institute for Health and Clinical Excellence (NICE); 2008 May. 37 p. (Clinical guideline; no. 67).

National Institute for Health and Clinical Excellence (NICE). Statins for the prevention of cardiovascular events. London (UK): National Institute for Health and Clinical Excellence (NICE); 2006 Jan. 45 p. (Technology appraisal guidance; no. 94).

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Clinical Guideline Centre (NCGC) on behalf of the National Institute for Health and Care Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance.

Recommendations are marked as [new 2014], [2014], [2008] or [2008, amended 2014]:

- [new 2014] indicates that the evidence has been reviewed and the recommendation has been added or updated
- [2014] indicates that the evidence has been reviewed but no change has been made to the recommended action
- [2008] indicates that the evidence has not been reviewed since 2008

- [2008, amended 2014] indicates that the evidence has not been reviewed since 2008, but changes have been made to the recommendation wording that change the meaning.

The wording used in the recommendations in this guideline (for example words such as 'offer' and 'consider') denotes the certainty with which the recommendation is made (the strength of the recommendation) and is defined at the end of the "Major Recommendations" field.

Identifying and Assessing Cardiovascular Disease (CVD) Risk

Identifying People for Full Formal Risk Assessment

For the primary prevention of CVD in primary care, use a systematic strategy to identify people who are likely to be at high risk. [2008, amended 2014]

Prioritise people on the basis of an estimate of their CVD risk before a full formal risk assessment. Estimate their CVD risk using CVD risk factors already recorded in primary care electronic medical records. [2008]

People older than 40 should have their estimate of CVD risk reviewed on an ongoing basis. [2008]

Prioritise people for a full formal risk assessment if their estimated 10-year risk of CVD is 10% or more. [2008, amended 2014]

Discuss the process of risk assessment with the person identified as being at risk, including the option of declining any formal risk assessment. [2008]

Do not use opportunistic assessment as the main strategy in primary care to identify CVD risk in unselected people. [2008]

Full Formal Risk Assessment

Be aware that all CVD risk assessment tools can provide only an approximate value for CVD risk. Interpretation of CVD risk scores should always reflect informed clinical judgement. [2008]

Use the QRISK2 risk assessment tool to assess CVD risk for the primary prevention of CVD in people up to and including age 84 years. [new 2014]

Do not use a risk assessment tool to assess CVD risk in people with type 1 diabetes. See "Primary Prevention for People with Type 1 Diabetes," below for advice on treatment with statins for people with type 1 diabetes. [new 2014] This recommendation updates and replaces a recommendation from the NICE guideline Type 1 diabetes: Diagnosis and management of type 1 diabetes in children, young people and adults (NICE clinical guideline 15).

Use the QRISK2 risk assessment tool to assess CVD risk in people with type 2 diabetes. [new 2014] This recommendation updates and replaces recommendations in the NICE guideline Type 2 diabetes. The management of type 2 diabetes (NICE clinical guideline 87).

Do not use a risk assessment tool to assess CVD risk in people with an estimated glomerular filtration rate (eGFR) less than 60 ml/min/1.73 m^2 and/or albuminuria*. These people are at increased risk of CVD. See recommendation below under "People with CKD" for advice on treatment with statins for people with chronic kidney disease (CKD). [new 2014]

Complete as many fields of the risk assessment tool as possible. [new 2014]

Routinely record ethnicity, body mass index and family history of premature CVD in medical records. [2008]

Consider socioeconomic status as an additional factor that contributes to CVD risk. [2008]

Do not use a risk assessment tool for people with pre-existing CVD. [2008, amended 2014]

Do not use a risk assessment tool for people who are at high risk of developing CVD because of familial hypercholesterolaemia (see the NGC summary of the NICE guideline Identification and management of familial hypercholesterolaemia [NICE clinical guideline 71]) or other inherited disorders of lipid metabolism. [2008, amended 2014]

When using the risk score to inform drug treatment decisions, particularly if it is near to the threshold for treatment, take into account other factors that:

- May predispose the person to premature CVD and

- May not be included in calculated risk scores. [2008, amended 2014]

Recognise that standard CVD risk scores will underestimate risk in people who have additional risk because of underlying medical conditions or treatments. These groups include:

- People treated for human immunodeficiency virus (HIV)
- People with serious mental health problems
- People taking medicines that can cause dyslipidaemia such as antipsychotic medication, corticosteroids or immunosuppressant drugs
- People with autoimmune disorders such as systemic lupus erythematosus, and other systemic inflammatory disorders. [2008, amended 2014]

Recognise that CVD risk will be underestimated in people who are already taking antihypertensive or lipid modification therapy, or who have recently stopped smoking. Use clinical judgement to decide on further treatment of risk factors in people who are below the CVD risk threshold for treatment. [2008, amended 2014]

Severe obesity (body mass index greater than 40 kg/m^2) increases CVD risk. Take this into account when using risk scores to inform treatment decisions in this group (see Obesity: Guidance on the prevention, identification, assessment and management of overweight and obesity in adults and children [NICE clinical guideline 43]). [2008]

Consider people aged 85 or older to be at increased risk of CVD because of age alone, particularly people who smoke or have raised blood pressure. [2008, amended 2014]

*People on renal replacement therapy are outside the scope of this guideline.

Communication About Risk Assessment and Treatment

NICE has produced guidance on the components of good patient experience in adult National Health Services (NHS) services. These include recommendations on the communication of risk. Follow the recommendations in Patient experience in adult NHS services (NICE clinical guidance 138). [new 2014]

Use everyday, jargon-free language to communicate information on risk. If technical terms are used, explain them clearly. [2008]

Set aside adequate time during the consultation to provide information on risk assessment and to allow any questions to be answered. Further consultation may be required. [2008]

Document the discussion relating to the consultation on risk assessment and the person's decision. [2008]

Offer people information about their absolute risk of CVD and about the absolute benefits and harms of an intervention over a 10-year period. This information should be in a form that:

- Presents individualised risk and benefit scenarios and
- Presents the absolute risk of events numerically and
- Uses appropriate diagrams and text. [2008]

To encourage the person to participate in reducing their CVD risk:

- Find out what, if anything, the person has already been told about their CVD risk and how they feel about it
- Explore the person's beliefs about what determines future health (this may affect their attitude to changing risk)
- Assess their readiness to make changes to their lifestyle (diet, physical activity, smoking and alcohol consumption), to undergo investigations and to take long-term medication
- Assess their confidence in making changes to their lifestyle, undergoing investigations and taking medication
- Inform them of potential future management based on current evidence and best practice
- Involve them in developing a shared management plan
- Check with them that they have understood what has been discussed. [2008, amended 2014]

If the person's CVD risk is at a level where intervention is recommended but they decline the offer of treatment, advise them that their CVD risk should be reassessed again in the future. Record their choice in their medical notes. [2008, amended 2014]

Lifestyle Modifications for the Primary and Secondary Prevention of CVD

Cardioprotective Diet

Advise people at high risk of or with CVD to eat a diet in which total fat intake is 30% or less of total energy intake, saturated fats are 7% or less of total energy intake, intake of dietary cholesterol is less than 300 mg/day and where possible saturated fats are replaced by mono-unsaturated and polyunsaturated fats. Further information and advice can be found at NHS Choices. [new 2014]

For people at high risk of or with CVD:

- Tell them that reducing their saturated fat intake from animal sources also reduces their mono-unsaturated fat levels.
- Advise them to replace their saturated and mono-unsaturated fat intake with olive oil, rapeseed oil or spreads based on these oils.
- Advise them to use olive oil, rapeseed oil or spreads based on these oils in food preparation.

Further information and advice on healthy cooking methods can be found at NHS Choices. [new 2014]

Advise people at high risk of or with CVD to do all of the following:

- Choose wholegrain varieties of starchy food
- Reduce their intake of sugar and food products containing refined sugars including fructose
- Eat at least 5 portions of fruit and vegetables per day
- Eat at least 2 portions of fish per week, including a portion of oily fish
- Eat at least 4 to 5 portions of unsalted nuts, seeds and legumes per week.

Further information and advice can be found at NHS Choices. [new 2014]

Advise pregnant women to limit their oily fish to no more than 2 portions per week and to avoid marlin, shark and swordfish. Further information and advice on oily fish consumption can be found at NHS Choices. [new 2014]

Take account of a person's individual circumstances – for example, drug therapy, comorbidities and other lifestyle modifications when giving dietary advice. [new 2014]

Advise and support people at high risk of or with CVD to achieve a healthy diet in line with Behaviour change: the principles for effective interventions (NICE public health guidance 6). [new 2014]

Physical Activity

Advise people at high risk of or with CVD to do the following every week:

- At least 150 minutes of moderate intensity aerobic activity or
- 75 minutes of vigorous intensity aerobic activity or a mix of moderate and vigorous aerobic activity

in line with national guidance for the general population (see Physical activity guidelines for adults at NHS Choices). [2008, amended 2014]

Advise people to do muscle-strengthening activities on 2 or more days a week that work all major muscle groups (legs, hips, back, abdomen, chest, shoulders and arms) in line with national guidance for the general population (see Physical activity guidelines for adults at NHS Choices). [new 2014]

Encourage people who are unable to perform moderate-intensity physical activity because of comorbidity, medical conditions or personal circumstances to exercise at their maximum safe capacity. [2008, amended 2014]

Advice about physical activity should take into account the person's needs, preferences and circumstances. Agree goals and provide the person with written information about the benefits of activity and local opportunities to be active, in line with Four commonly used methods to increase physical activity (NICE public health guidance 2). [2008]

Combined Interventions (Diet and Physical Activity)

Give advice on diet and physical activity in line with national recommendations (see NHS Choices). [2008]

Weight Management

Offer people at high risk of or with CVD who are overweight or obese appropriate advice and support to work towards achieving and maintaining

a healthy weight, in line with Obesity: Guidance on the prevention, identification, assessment and management of overweight and obesity in adults and children (NICE clinical guideline 43). [2008]

Alcohol Consumption

Be aware that men should not regularly drink more than 3–4 units a day and women should not regularly drink more than 2–3 units a day. People should avoid binge drinking. Further information can be found at NHS Choices. [2008]

Smoking Cessation

Advise all people who smoke to stop, in line with Smoking cessation services (NICE public health guidance 10). [2008]

Offer people who want to stop smoking support and advice, and referral to an intensive support service (for example, the NHS Stop Smoking Services). [2008]

If a person is unable or unwilling to accept a referral to an intensive support service, offer them pharmacotherapy in line with Smoking cessation services (NICE public health guidance 10) and Varenicline for smoking cessation (NICE technology appraisal guidance 123). [2008]

Plant Stanols and Sterols

Do not advise any of the following to take plant stanols or sterols for the prevention of CVD:

- People who are being treated for primary prevention
- People who are being treated for secondary prevention
- People with chronic kidney disease (CKD)
- People with type 1 diabetes
- People with type 2 diabetes. [new 2014]

Lipid Modification Therapy for the Primary and Secondary Prevention of CVD

Be aware that when deciding on lipid modification therapy for the prevention of CVD, drugs are preferred for which there is evidence in clinical trials of a beneficial effect on CVD morbidity and mortality. [2008]

When a decision is made to prescribe a statin use a statin of high intensity and low acquisition cost. (See appendix A in the original guideline document for statin classification.) [new 2014]

Lipid Measurement and Referral

Recommendations in this section update and replace a recommendation in the NICE guideline Type 2 diabetes. The management of type 2 diabetes (NICE clinical guideline 87).

Measure both total and high-density lipoprotein (HDL) cholesterol to achieve the best estimate of CVD risk. [2008]

Before starting lipid modification therapy for the primary prevention of CVD, take at least 1 lipid sample to measure a full lipid profile. This should include measurement of total cholesterol, HDL cholesterol, non-HDL cholesterol and triglyceride concentrations. A fasting sample is not needed. [new 2014]

Use the clinical findings, lipid profile and family history to judge the likelihood of a familial lipid disorder rather than the use of strict lipid cut-off values alone. [new 2014]

Exclude possible common secondary causes of dyslipidaemia (such as excess alcohol, uncontrolled diabetes, hypothyroidism, liver disease and nephrotic syndrome) before referring for specialist review. [new 2014]

Consider the possibility of familial hypercholesterolaemia and investigate as described in the NGC summary of the NICE guideline Identification and management of familial hypercholesterolaemia (NICE clinical guideline 71) if they have:

- A total cholesterol concentration more than 7.5 mmol/litre and
- A family history of premature coronary heart disease. [new 2014]

Arrange for specialist assessment of people with a total cholesterol concentration of more than 9.0 mmol/litre or a non-HDL cholesterol concentration of more than 7.5 mmol/litre even in the absence of a first-degree family history of premature coronary heart disease. [new 2014]

Refer for urgent specialist review if a person has a triglyceride concentration of more than 20 mmol/litre that is not a result of excess alcohol or poor glycaemic control. [new 2014]

In people with a triglyceride concentration between 10 and 20 mmol/litre:

- Repeat the triglyceride measurement with a fasting test (after an interval of 5 days, but within 2 weeks) and
- Review for potential secondary causes of hyperlipidaemia and
- Seek specialist advice if the triglyceride concentration remains above 10 mmol/litre. [new 2014]

In people with a triglyceride concentration between 4.5 and 9.9 mmol/litre:

- Be aware that the CVD risk may be underestimated by risk assessment tools and
- Optimise the management of other CVD risk factors present and
- Seek specialist advice if non-HDL cholesterol concentration is more than 7.5 mmol/litre. [new 2014]

Statins for the Prevention of CVD

Recommendations in this section update and replace those in Statins for the prevention of cardiovascular events (NICE technology appraisal guidance 94).

The decision whether to start statin therapy should be made after an informed discussion between the clinician and the person about the risks and benefits of statin treatment, taking into account additional factors such as potential benefits from lifestyle modifications, informed patient preference, comorbidities, polypharmacy, general frailty and life expectancy. [new 2014]

Before starting statin treatment perform baseline blood tests and clinical assessment, and treat comorbidities and secondary causes of dyslipidaemia. Include all of the following in the assessment:

- Smoking status
- Alcohol consumption
- Blood pressure (see the NGC summary of the NICE guideline Hypertension. Clinical management of primary hypertension in adults [NICE clinical guideline 127])
- Body mass index or other measure of obesity (see Obesity: Guidance on the prevention, identification, assessment and management of overweight and obesity in adults and children [NICE clinical guideline 43])
- Total cholesterol, non-HDL cholesterol, HDL cholesterol and triglycerides
- Glycosylated hemoglobin (HbA_{1c})
- Renal function and eGFR
- Transaminase level (alanine aminotransferase or aspartate aminotransferase)
- Thyroid-stimulating hormone. [new 2014]

Primary Prevention

Before offering statin treatment for primary prevention, discuss the benefits of lifestyle modification and optimise the management of all other modifiable CVD risk factors if possible. [new 2014]

Recognise that people may need support to change their lifestyle. To help them do this, refer them to programmes such as exercise referral schemes (see Behaviour change: individual approaches [NICE public health guidance 49]). [new 2014]

Offer people the opportunity to have their risk of CVD assessed again after they have tried to change their lifestyle. [new 2014]

If lifestyle modification is ineffective or inappropriate offer statin treatment after risk assessment. [new 2014]

Offer atorvastatin 20 mg for the primary prevention of CVD to people who have a 10% or greater 10-year risk of developing CVD. Estimate the level of risk using the QRISK2 assessment tool. [new 2014]

For people 85 years or older consider atorvastatin 20 mg as statins may be of benefit in reducing the risk of non-fatal myocardial infarction. Be aware of factors that may make treatment inappropriate (see recommendation in the previous section). [new 2014]

Secondary Prevention

Start statin treatment in people with CVD with atorvastatin 80 mg†. Use a lower dose of atorvastatin if any of the following apply:

- Potential drug interactions
- High risk of adverse effects
- Patient preference. [new 2014]

Do not delay statin treatment in secondary prevention to manage modifiable risk factors. [2014]

If a person has acute coronary syndrome, do not delay statin treatment. Take a lipid sample on admission and about 3 months after the start of treatment. [2008, amended 2014]

†Note: At the time of publication (July 2014), atorvastatin did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing and managing medicines and devices for further information.

Primary Prevention for People with Type 1 Diabetes

Recommendations in this section update and replace recommendations from Type 1 diabetes: Diagnosis and management of type 1 diabetes in children, young people and adults (NICE clinical guideline 15).

Consider statin treatment for the primary prevention of CVD in all adults with type 1 diabetes. [new 2014]

Offer statin treatment for the primary prevention of CVD to adults with type 1 diabetes who:

- Are older than 40 years or
- Have had diabetes for more than 10 years or
- Have established nephropathy or
- Have other CVD risk factors. [new 2014]

Start treatment for adults with type 1 diabetes with atorvastatin 20 mg. [new 2014]

Primary Prevention for People with Type 2 Diabetes

Offer atorvastatin 20 mg for the primary prevention of CVD to people with type 2 diabetes who have a 10% or greater 10-year risk of developing CVD. Estimate the level of risk using the QRISK2 assessment tool. [new 2014] This recommendation updates and replaces recommendations in the NICE guideline Type 2 diabetes. The management of type 2 diabetes (NICE clinical guideline 87).

People with CKD

Offer atorvastatin 20 mg for the primary or secondary prevention of CVD to people with CKD (see the NGC summary of the NICE guideline Chronic kidney disease. Early identification and management of chronic kidney disease in adults in primary and secondary care for CKD classification [NICE clinical guideline 182]). People on renal replacement therapy are outside the scope of this guideline.)

- Increase the dose if a greater than 40% reduction in non-HDL cholesterol is not achieved (see recommendation in the following section) and eGFR is 30 ml/min/1.73 m^2 or more.
- Agree the use of higher doses with a renal specialist if eGFR is less than 30 ml/min/1.73 m^2. [new 2014]

Follow-up of People Started on Statin Treatment

Measure total cholesterol, HDL cholesterol and non-HDL cholesterol in all people who have been started on high-intensity statin treatment at 3 months of treatment and aim for a greater than 40% reduction in non-HDL cholesterol. If a greater than 40% reduction in non-HDL cholesterol is not achieved:

- Discuss adherence and timing of dose
- Optimise adherence to diet and lifestyle measures
- Consider increasing the dose if started on less than atorvastatin 80 mg and the person is judged to be at higher risk because of comorbidities, risk score or using clinical judgement. [new 2014]

This recommendation updates and replaces a recommendation from Type 1 diabetes: Diagnosis and management of type 1 diabetes in children, young people and adults (NICE clinical guideline 15).

Provide annual medication reviews for people taking statins.

- Use these reviews to discuss medicines adherence and lifestyle modification and address CVD risk factors.
- Consider an annual non-fasting blood test for non-HDL cholesterol to inform the discussion. [new 2014]

Discuss with people who are stable on a low- or middle-intensity statin the likely benefits and potential risks of changing to a high-intensity statin when they have a medication review and agree with the person whether a change is needed. [new 2014]

Advice and Monitoring for Adverse Effects

Advise people who are being treated with a statin:

- That other drugs, some foods (for example, grapefruit juice) and some supplements may interfere with statins and
- To always consult the patient information leaflet, a pharmacist or prescriber for advice when starting other drugs or thinking about taking supplements. [new 2014]

Remind the person to restart the statin if they stopped taking it because of drug interactions or to treat intercurrent illnesses. [new 2014]

Before offering a statin, ask the person if they have had persistent generalised unexplained muscle pain, whether associated or not with previous lipid-lowering therapy. If they have, measure creatine kinase levels.

- If creatine kinase levels are more than 5 times the upper limit of normal, re-measure creatine kinase after 7 days. If creatine kinase levels are still 5 times the upper limit of normal, do not start statin treatment.
- If creatine kinase levels are raised but less than 5 times the upper limit of normal, start statin treatment at a lower dose. [new 2014]

Advise people who are being treated with a statin to seek medical advice if they develop muscle symptoms (pain, tenderness or weakness). If this occurs, measure creatine kinase. [2008]

If people report muscle pain or weakness while taking a statin, explore other possible causes of muscle pain or weakness and raised creatine kinase if they have previously tolerated statin therapy for more than 3 months. [new 2014]

Do not measure creatine kinase levels in asymptomatic people who are being treated with a statin. [2008]

Measure baseline liver transaminase enzymes (alanine aminotransferase or aspartate aminotransferase) before starting a statin. Measure liver transaminase within 3 months of starting treatment and at 12 months, but not again unless clinically indicated. [2008]

Do not routinely exclude from statin therapy people who have liver transaminase levels that are raised but are less than 3 times the upper limit of normal. [2008]

Do not stop statins because of an increase in blood glucose level or HbA_{1c} (see the recommendations on assessing for risk of diabetes mellitus in Preventing type 2 diabetes: risk identification and interventions for individuals at high risk [NICE public health guidance 38]). [new 2014]

Statins are contraindicated in pregnancy:

- Advise women of childbearing potential of the potential teratogenic risk of statins and to stop taking them if pregnancy is a possibility.

Advise women planning pregnancy to stop taking statins 3 months before they attempt to conceive and to not restart them until breastfeeding is finished. [new 2014]

This recommendation updates and replaces a recommendation from the NICE guideline Type 2 diabetes. The management of type 2 diabetes (NICE clinical guideline 87).

Intolerance of Statins

If a person is not able to tolerate a high-intensity statin aim to treat with the maximum tolerated dose. [new 2014]

Tell the person that any statin at any dose reduces CVD risk. If someone reports adverse effects when taking high-intensity statins discuss the following possible strategies with them:

- Stopping the statin and trying again when the symptoms have resolved to check if the symptoms are related to the statin
- Reducing the dose within the same intensity group

- Changing the statin to a lower intensity group. [new 2014]

Seek specialist advice about options for treating people at high risk of CVD such as those with CKD, type 1 diabetes, type 2 diabetes or genetic dyslipidaemias, and those with CVD, who are intolerant to 3 different statins. Advice can be sought for example, by telephone, virtual clinic or referral. [new 2014]

Adherence to Statin Therapy

Do not offer coenzyme Q10 or vitamin D to increase adherence to statin treatment. [new 2014]

Fibrates for Preventing CVD

Do not routinely offer fibrates for the prevention of CVD to any of the following:

- People who are being treated for primary prevention
- People who are being treated for secondary prevention
- People with CKD
- People with type 1 diabetes
- People with type 2 diabetes [new 2014]

This recommendation updates and replaces recommendations in the NICE guideline Type 2 diabetes. The management of type 2 diabetes (NICE clinical guideline 87) and recommendations from Type 1 diabetes: Diagnosis and management of type 1 diabetes in children, young people and adults (NICE clinical guideline 15).

Nicotinic Acid for Preventing CVD

Do not offer nicotinic acid (niacin) for the prevention of CVD to any of the following:

- People who are being treated for primary prevention
- People who are being treated for secondary prevention
- People with CKD
- People with type 1 diabetes
- People with type 2 diabetes. [new 2014]

This recommendation updates and replaces recommendations from Type 1 diabetes: Diagnosis and management of type 1 diabetes in children, young people and adults (NICE clinical guideline 15) and from the NICE guideline Type 2 diabetes. The management of type 2 diabetes (NICE clinical guideline 87).

Bile Acid Sequestrants (Anion Exchange Resins) for Preventing CVD

Do not offer a bile acid sequestrant (anion exchange resin) for the prevention of CVD to any of the following:

- People who are being treated for primary prevention
- People who are being treated for secondary prevention
- People with CKD
- People with type 1 diabetes
- People with type 2 diabetes. [new 2014]

This recommendation updates and replaces a recommendation from Type 1 diabetes: Diagnosis and management of type 1 diabetes in children, young people and adults (NICE clinical guideline 15).

Omega-3 Fatty Acid Compounds for Preventing CVD

Recommendations in this section update and replace recommendations in the NICE guideline Type 2 diabetes. The management of type 2 diabetes (NICE clinical guideline 87).

Do not offer omega-3 fatty acid compounds for the prevention of CVD to any of the following:

- People who are being treated for primary prevention
- People who are being treated for secondary prevention

- People with CKD
- People with type 1 diabetes
- People with type 2 diabetes. [new 2014]

Tell people that there is no evidence that omega-3 fatty acid compounds help to prevent CVD. [new 2014]

Combination Therapy for Preventing CVD

Do not offer the combination of a bile acid sequestrant (anion exchange resin), fibrate, nicotinic acid or omega-3 fatty acid compound with a statin for the primary or secondary prevention of CVD. [new 2014]

Ezetimibe

People with primary hypercholesterolaemia should be considered for ezetimibe treatment in line with Ezetimibe for the treatment of primary (heterozygous familial and non-familial) hypercholesterolaemia (NICE technology appraisal guidance 132). [2008]

Definitions:

Strength of Recommendations

Some recommendations can be made with more certainty than others. The Guideline Development Group (GDG) makes a recommendation based on the trade-off between the benefits and harms of an intervention, taking into account the quality of the underpinning evidence. For some interventions, the GDG is confident that, given the information it has looked at, most patients would choose the intervention. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the strength of the recommendation).

Interventions That Must (or Must Not) Be Used

The GDG usually uses 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally the GDG uses 'must' (or 'must not') if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

Interventions That Should (or Should Not) Be Used – a 'Strong' Recommendation

The GDG uses 'offer' (and similar words such as 'refer' or 'advise') when confident that, for the vast majority of patients, an intervention will do more good than harm, and be cost effective. Similar forms of words (for example, 'Do not offer…') are used when the GDG is confident that an intervention will not be of benefit for most patients.

Interventions That Could Be Used

The GDG uses 'consider' when confident that an intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.

Note: The National Institute for Health and Care Excellence (NICE) began using this approach to denote the strength of recommendations in guidelines that started development after publication of the 2009 version of 'The guidelines manual' (January 2009). This does not apply to any recommendations ending [2008]. In particular, for recommendations labelled [2008] the word 'consider' may not necessarily be used to denote the strength of the recommendation.

Clinical Algorithm(s)

A National Institute for Health and Care Excellence (NICE) pathway titled "Cardiovascular Disease Prevention Overview" is available on the NICE Web site.

Scope

Disease/Condition(s)

- Cardiovascular disease (CVD)
- Dyslipidemia
- Hypercholesterolaemia

Guideline Category

Prevention

Risk Assessment

Treatment

Clinical Specialty

Cardiology

Family Practice

Geriatrics

Internal Medicine

Preventive Medicine

Intended Users

Advanced Practice Nurses

Dietitians

Health Care Providers

Nurses

Patients

Physician Assistants

Physicians

Guideline Objective(s)

- To provide updated recommendations on identification and risk assessment for cardiovascular disease (CVD) and on the use of lipid-lowering drugs
- To allow consideration of new evidence on risk assessment tools and to reflect changes in price and availability of generic statins

Target Population

- Adults (aged 18 years and older) without established cardiovascular disease (CVD)
- Adults with type 1 diabetes
- Adults with type 2 diabetes
- Adults with chronic kidney disease (CKD)
- Adults (aged 18 and older) with established CVD
- The following special groups are considered:
    - People from black and minority ethnic groups
    - People with a family history of CVD

- People from low socioeconomic groups
- People older than 75
- Women
- People with autoimmune disease
- People with serious mental illness

Note: The guideline does not cover:

Children and young people (aged 18 years and younger)
People with familial hypercholesterolaemia
People with familial clotting disorders that increase cardiovascular risk
People with other genetic disorders that increase cardiovascular risk
People at high risk of CVD or abnormalities of lipid metabolism as a result of endocrine or other secondary disease processes other than diabetes
People receiving renal replacement therapy

Interventions and Practices Considered

1. Identifying and assessing cardiovascular disease (CVD) risk
    - Identifying people for full formal risk assessment
    - Use of the QRISK2 risk assessment tool
    - Communication with patients about risk assessment and treatment
2. Lifestyle modifications for primary and second prevention of CVD
    - Cardioprotective diet
    - Physical activity
    - Combined interventions (diet and physical activity)
    - Weight management
    - Smoking cessation
    - Limiting alcohol consumption
    - Advice on plant stanols or sterols
3. Lipid modification therapy for primary and secondary prevention of CVD
    - Lipid measurement and referral to specialist as needed (measurement of total cholesterol, high-density lipoprotein [HDL] cholesterol, non-HDL cholesterol and triglyceride concentrations)
    - Statins for primary and secondary prevention
    - Primary prevention for people with type 1 and type 2 diabetes (atorvastatin)
    - Primary and secondary prevention in people with chronic kidney disease (atorvastatin)
    - Follow-up of people started on statin treatment
    - Advice and monitoring of adverse effects of statin treatment
    - Management of statin intolerance
    - Ezetimibe

Note: The following were considered but not recommended for prevention of CVD:

Fibrate therapy (not recommended routinely)
Nicotinic acid therapy
Bile acid sequestrants (anion exchange resins)
Omega-3 fatty acid compounds
Combination therapy of a bile acid sequestrant (anion exchange resin), fibrate, nicotinic acid or omega-3 fatty acid compound with a statin

Major Outcomes Considered

- Sensitivity, specificity, and predictive value of assessment tools
- Mortality (all-cause, cardiovascular)
- Sudden cardiac death

- Incidence of myocardial infarction, cerebrovascular accident, transient ischemic attack, or stroke
- 10-year risk of developing cardiovascular disease (CVD)
- Lifetime risk of developing CVD
- Hospitalization rate
- Adverse events
- Quality of life
- Adherence
- Cost-effectiveness

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Clinical Guideline Centre (NCGC) on behalf of the National Institute for Health and Care Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance.

Developing the Review Questions and Outcomes

Review questions were developed in a PICO framework (patient, intervention, comparison and outcome) for intervention reviews. Prognostic questions were developed in a framework of population, presence or absence of factors under investigation (for example prognostic factors) and outcomes.

This use of a framework guided the literature searching process, critical appraisal and synthesis of evidence, and facilitated the development of recommendations by the Guideline Development Group (GDG). The review questions were drafted by the NCGC technical team and refined and validated by the GDG. The questions were based on the key clinical issues identified in the scope (Appendix A in the full version of the original guideline document).

A total of 11 review questions were identified.

Full literature searches, critical appraisals and evidence reviews were completed for all the specified review questions.

Searching for Evidence

Clinical Literature Search

Systematic literature searches were undertaken to identify all published clinical evidence relevant to the review questions. Searches were undertaken according to the parameters stipulated within the NICE guidelines manual 2012 (see the "Availability of Companion Documents" field). Databases were searched using relevant medical subject headings and free-text terms. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to articles published in English. All searches were conducted in MEDLINE, EMBASE, and The Cochrane Library, and were updated for the final time on 11 November 2013. No papers published after this date were considered.

Search strategies were quality assured by cross-checking reference lists of highly relevant papers, analysing search strategies in other systematic reviews, and asking GDG members to highlight any additional studies. The questions, the study types applied, the databases searched and the years covered can be found in Appendix F in the full version of the original guideline document.

The titles and abstracts of records retrieved by the searches were sifted for relevance, with potentially significant publications obtained in full text. These were assessed against the inclusion criteria.

Health Economics Literature Search

Systematic searches were also undertaken to identify relevant health economic evidence within published literature relevant to the review questions. The evidence was identified by conducting a broad search relating to cardiovascular disease (CVD) in the National Health Service (NHS) Economic Evaluation Database (NHS EED), the Health Technology Assessment database (HTA) and the Health Economic Evaluations Database (HEED) with no date restrictions. Additionally, the search was run on MEDLINE and EMBASE using a specific economic filter, from 2010, to ensure recent publications that not yet been indexed by the economic databases were identified. This was supplemented by an additional search that looked for economic papers specifically relating to fibrates, bile acid sequestrants, nicotinic acids, omega-3 fatty acids, or phytosterols and phytostanols on the same databases. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to articles published in English.

The health economics search strategies are included in Appendix F in the full version of the original guideline document. All searches were updated on 11 November 2013. No papers published after this date were considered.

Evidence of Effectiveness

Overview of Reviewing the Evidence of Effectiveness

The evidence was reviewed following the steps shown schematically in Figure 1 in the full version of the original guideline document:

- Potentially relevant studies were identified for each review question from the relevant search results by reviewing titles and abstracts. Full papers were then obtained.
- Full papers were reviewed against prespecified inclusion and exclusion criteria to identify studies that addressed the review question in the appropriate population (review protocols are included in Appendix C in the full version of the original guideline document).

Inclusion and Exclusion Criteria

The inclusion and exclusion of studies was based on the review protocols, which can be found in Appendix C in the full version of the original guideline document. Excluded studies by review question (with the reasons for their exclusion) are listed in Appendix J in the full version of the original guideline document. The GDG was consulted about any uncertainty regarding inclusion or exclusion.

The guideline population encompassed adults aged 18 or older in the following groups:

- People at high risk of CVD (primary prevention population)
- People with type 1 diabetes mellitus
- People with type 2 diabetes mellitus
- People with chronic kidney disease
- People with CVD including people with prior myocardial infarction (MI), prior stroke, peripheral arterial disease, angina (secondary prevention population)

Evidence was also sought and included for the following special groups for each review question.

- People from black and minority ethnic groups
- People with a family history of CVD
- People from low socioeconomic groups
- People older than 75 years
- Women
- People with autoimmune disease
- People with serious mental illness

Randomised trials, non-randomised trials, and observational studies (including prognostic studies) were included in the evidence reviews as appropriate.

Conference abstracts were not automatically excluded from the review but were initially assessed against the inclusion criteria and then further processed only if either no other full publication was available for that review question or if the GDG considered the abstract sufficiently important to inform recommendations. One abstract of a published study which reported additional outcomes was included in the review of nicotinic acids.

The search for the review of efficacy of statin therapy identified a systematic review that the GDG considered relevant to the question. The GDG decided that further data were required to inform recommendations and the authors contacted for the information.

Literature reviews, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded.

Evidence of Cost-effectiveness

The GDG is required to make decisions based on the best available evidence of both clinical and cost effectiveness. Guideline recommendations should be based on the expected costs of the different options in relation to their expected health benefits (that is, their 'cost effectiveness') rather than the total implementation cost. Thus, if the evidence suggests that a strategy provides significant health benefits at an acceptable cost per patient treated, it should be recommended even if it would be expensive to implement across the whole population.

Evidence on cost effectiveness related to the key clinical issues being addressed in the guideline was sought. The health economist:

- Undertook a systematic review of the published economic literature.
- Undertook new cost-effectiveness analysis in the highest priority area.

Literature Review

The health economist:

- Identified potentially relevant studies for each review question from the economic search results by reviewing titles and abstracts. Full papers were then obtained.
- Reviewed full papers against pre-specified inclusion and exclusion criteria to identify relevant studies (see the full version of the original guideline document for details).

Inclusion and Exclusion Criteria

Full economic evaluations (studies comparing costs and health consequences of alternative courses of action: cost–utility, cost-effectiveness, cost–benefit and cost–consequence analyses) and comparative costing studies that addressed the review question in the relevant population were considered potentially includable as economic evidence.

Studies that only reported cost per hospital (not per patient), or only reported average cost effectiveness without disaggregated costs and effects, were excluded. Literature reviews, abstracts, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded.

Remaining studies were prioritised for inclusion based on their relative applicability to the development of this guideline and the study limitations. For example, if a high quality, directly applicable United Kingdom (UK) analysis was available, then other less relevant studies may not have been included. Where exclusions occurred on this basis, this is noted in the relevant section.

For more details about the assessment of applicability and methodological quality see the economic evaluation checklist (Appendix F of The Guidelines Manual [see the "Availability of Companion Documents" field] and the health economics review protocol in Appendix C in the full version of the original guideline document).

When no relevant economic studies were found from the economic literature review, relevant UK NHS unit costs related to the compared interventions were presented to the GDG to inform the possible economic implications of the recommendations.

Number of Source Documents

Refer to Appendix D in the full version of the original guideline document (see the "Availability of Companion Documents" field) for flow diagrams of clinical selection, which detail the total number of studies included for each guideline topic.

Refer to Appendix E in the full version of the original guideline document (see the "Availability of Companion Documents" field) for a flow diagram of economic article selection for the guideline.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Overall Quality of Outcome Evidence in Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Level	Description
High	Further research is very unlikely to change confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Very Low	Any estimate of effect is very uncertain.

Methods Used to Analyze the Evidence

Meta-Analysis of Randomized Controlled Trials

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Clinical Guideline Centre (NCGC) on behalf of the National Institute for Health and Care Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance.

Evidence of Effectiveness

Relevant studies were critically appraised using the appropriate checklist as specified in The Guidelines Manual (see the "Availability of Companion Documents" field).

Key information was extracted on the study's methods and PICO (population, intervention, comparison, outcome) factors and results were presented in evidence tables (see Appendix G of the full version of the original guideline document).

Summaries of evidence were generated by outcome (included in the relevant review chapters) and were presented in Guideline Development Group (GDG) meetings:

- Randomised studies: data were meta-analysed where appropriate and reported in GRADE profiles (for intervention reviews).
- Prognostic studies: data were presented as a range of values including; sensitivity and specificity at various thresholds, coupled values of sensitivity and specificity summarised in receiver operating curves (ROC) to allow visual comparison between different index tests (plotting data at different thresholds) and to investigate heterogeneity more effectively, area under ROC curve (AUC) (as reported by the authors), and ratio of predicted versus observed events. Meta-analyses could not be conducted because the studies reported data at various thresholds.

A 20% sample of each of the above stages of the reviewing process was quality assured by a second reviewer to eliminate any potential of reviewer bias or error.

Methods of Combining Studies

Data Synthesis for Intervention Reviews

Where possible, meta-analyses were conducted to combine the results of studies for each review question using Cochrane Review Manager (RevMan5) software. Fixed-effects (Mantel-Haenszel) techniques were used to calculate pooled risk ratios (relative risk) for binary outcomes.

For continuous outcomes, measures of central tendency (mean) and variation (standard deviation [SD]) were required for meta-analysis. Data for continuous outcomes were analysed using an inverse variance method for pooling mean differences, and where the studies had different scales, standardised mean differences were used. A generic inverse variance option in Review Manager was used if any studies reported solely the

summary statistics and 95% confidence interval (or standard error); this included any hazard ratios reported. However, in cases where standard deviations were not reported per intervention group, the standard error (SE) for the mean difference was calculated from other reported statistics: p-values or 95% confidence intervals (95% CI); meta-analysis was then undertaken for the mean difference and standard error using the generic inverse variance method in Cochrane Review Manager (RevMan5) software. When the only evidence was based on studies that summarised results by presenting medians (and interquartile ranges), or only p-values were given, this information was assessed in terms of the study's sample size and was included in the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tables without calculating the relative or absolute effects. Consequently, aspects of quality assessment such as imprecision of effect could not be assessed for evidence of this type.

Stratified analyses were predefined for the majority of questions at the protocol stage according to population; primary prevention, type 1 diabetes mellitus, type 2 diabetes mellitus, chronic kidney disease and secondary prevention. The GDG identified that these strata are different in terms of biological and clinical characteristics and the interventions could be expected to have a different effect.

Statistical heterogeneity was assessed by visually examining the forest plots, and by considering the chi-squared test for significance at $p<0.1$ and the I-squared inconsistency statistic (with an I-squared value of more than 50% indicating considerable heterogeneity). Where considerable heterogeneity was present, the guideline developers carried out sensitivity analyses. Pre-specified groups were defined for the review question on efficacy of statin therapy. These included: intensity of statin therapy, population, length of follow-up and specific drug and dose.

For interpretation of the binary outcome results, differences in the absolute event rate were calculated using the GRADEpro software, for the median event rate across the control arms of the individual studies in the meta-analysis. Absolute risk differences were presented in the GRADE profiles and in clinical summary of findings tables, for discussion with the GDG.

Data Synthesis for Prognostic Reviews

Meta-analyses could not be conducted for the review question on risk assessment because the studies reported data at various thresholds. The GDG decided that the results for each risk tool and outcome should be presented separately. The GDG used the results from prognostic studies and a health economic model to decide the clinically acceptable thresholds for the review question on statin therapy.

Types of Studies

For most intervention reviews in this guideline, parallel randomised controlled trials (RCTs) were included because they are considered the most robust type of study design that could produce an unbiased estimate of the intervention effects. Crossover RCTs were not included. If the GDG believed RCT data would not be appropriate or there was limited evidence from RCTs, best available quality non-randomised studies were to be included (please refer to Appendix F in the full version of the original guideline document for full details on the study design of studies selected per review question). For example, case series were the option of study design for the review question on prediction of statin adverse effects.

For the prognostic reviews on risk assessment tools, outcomes were extracted for each study and meta-analysis was not conducted.

Types of Analysis

Estimates of effect from individual studies were based on available case analysis (ACA): that is, analysing only data that were available for participants at the end of follow-up, without making any imputations for missing data. The GDG recorded several potential reasons for people dropping out before trial completion:

- Adverse effects
- Lack of concordance (adherence)
- Investigator's discretion (this is usually not defined in the studies but is likely to include clinical or laboratory-determined adverse events, or laboratory abnormalities meaning the drug may be contraindicated, or development of mutations).

The ACA method was used rather than an intention-to-treat with imputation analysis (ITT), in order to avoid making assumptions about the participants for whom outcome data was not available, and furthermore assuming that those with missing outcome data have the same event rate as those who continue. In addition, ITT analysis tends to bias the results towards no difference, and therefore the effect may be smaller than in reality. Using ACA, the guideline developers avoided incorrectly weighting studies in meta-analysis by using a denominator that does not reflect the true sample size with outcome data available. If there was a differential missing data rate between the 2 arms in a study greater than 10%, a sensitivity analysis was performed to determine whether the size and direction of effect would be changed by using an ITT or ACA analysis and whether there was an impact on the meta-analysis. If this were the case, a footnote was added to the GRADE tables to describe the dependence on the assumptions, and results from both ACA and ITT analyses were presented in the forest plots section (see Appendix I in the full version of the original guideline document). However, the majority of trials included in the review of evidence for this guideline (98%) had less than 5% differential missing outcome data.

When the studies reported only ITT results (through imputation), and the number of events was larger than the number of completers in the trial (ACA), the guideline developers then used the proportion of events from the ITT numbers to derive the number of events for the final sample size of completers. In the cases where it was not possible to extract data from the studies on ACA and authors reported only an ITT analysis, then the results of this analysis was included and a footnote was added to the GRADE tables.

Refer to section 3 in the full version of the original guideline document for additional discussion of statistical methods used in analyzing the evidence of effectiveness.

Appraising the Quality of the Evidence by Outcomes

The evidence for outcomes from the included RCTs and, where appropriate, observational studies was evaluated and presented using the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group (http://www.gradeworkinggroup.org/). The software (GRADEpro) developed by the GRADE working group was used to assess the evidence quality for each outcome, taking into account individual study quality factors and the meta-analysis results. Results were presented in GRADE profiles ('GRADE tables') which consist of 2 sections: the 'Clinical evidence profile' table includes details of the quality assessment while the 'Clinical evidence summary of findings' table includes pooled outcome data, where appropriate, an absolute measure of the intervention effect and the summary of quality of evidence for that outcome. In this table, the columns for intervention and control indicate summary measures and measures of dispersion (such as mean and standard deviation or median and range) for continuous outcomes and frequency of events (n/N: the sum across studies of the number of patients with events divided by sum of the number of completers) for binary outcomes. Reporting or publication bias was only taken into consideration in the quality assessment and included in the 'Clinical evidence profile' table if it was apparent (using funnel plots for more than 4 studies).

The evidence for each outcome was examined separately for the quality elements listed and defined in Table 2 in the full version of the original guideline document. Each element was graded using the quality levels listed in Table 3 in the full version of the original guideline document. The main criteria considered in the rating of these elements are discussed below. Footnotes were used to describe reasons for grading a quality element as having serious or very serious problems. The ratings for each component were summed to obtain an overall assessment for each outcome (Table 4 in the full version of the original guideline document).

Grading the Quality of Clinical Evidence

After results were pooled, the overall quality of evidence for each outcome was considered. The following procedure was adopted when using GRADE:

1. A quality rating was assigned, based on the study design. RCTs start as High and observational studies as Low, uncontrolled case series as Low or Very low.
2. The rating was then downgraded for the specified criteria: risk of bias (study limitations), inconsistency, indirectness, imprecision and publication bias. These criteria are detailed below. Evidence from observational studies (which had not previously been downgraded) was upgraded if there was: a large magnitude of effect, a dose–response gradient, and if all plausible confounding would reduce a demonstrated effect or suggest a spurious effect when results showed no effect. Each quality element considered to have "serious" or "very serious" risk of bias was rated at 1 or 2 points respectively.
3. The downgraded or upgraded marks were then summed and the overall quality rating was revised. For example, all RCTs started as High and the overall quality became Moderate, Low or Very low if 1, 2 or 3 points were deducted respectively.
4. The reasons or criteria used for downgrading were specified in the footnotes.

The details of criteria used for each of the main quality elements are discussed further in section 3 in the full version of the original guideline document.

Evidence of Cost-effectiveness

Literature Review

The health economist:

- Critically appraised relevant studies using the economic evaluations checklist as specified in The Guidelines Manual (see the "Availability of Companion Documents" field).
- Extracted key information about the studies' methods and results into evidence tables (included in Appendix H in the full version of the original guideline document).
- Generated summaries of the evidence in NICE economic evidence profiles (included in the relevant chapter for each review question) – see

the full version of the original guideline document for details.

NICE Economic Evidence Profiles

The NICE economic evidence profile has been used to summarise cost and cost-effectiveness estimates. The economic evidence profile shows an assessment of applicability and methodological quality for each economic evaluation, with footnotes indicating the reasons for the assessment. These assessments were made by the health economist using the economic evaluation checklist from The Guidelines Manual. It also shows the incremental costs, incremental effects (for example, quality-adjusted life years [QALYs]) and incremental cost-effectiveness ratio for the base case analysis in the evaluation, as well as information about the assessment of uncertainty in the analysis. See Table 6 in the full version of the original guideline document for more details.

If a non-United Kingdom (UK) study was included in the profile, the results were converted into pounds sterling using the appropriate purchasing power parity.

In the Absence of Economic Evidence

When no relevant published studies were found, and a new analysis was not prioritised, the GDG made a qualitative judgement about cost-effectiveness by considering expected differences in resource use between options and relevant UK National Health Service unit costs, alongside the results of the clinical review of effectiveness evidence.

Methods Used to Formulate the Recommendations

Expert Consensus

Informal Consensus

Description of Methods Used to Formulate the Recommendations

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Clinical Guideline Centre (NCGC) for Primary Care on behalf of the National Institute for Health and Care Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance.

A multidisciplinary Guideline Development Group (GDG) comprising health professionals and researchers as well as lay members developed this guideline. The group met every 5-8 weeks during the development of the guideline.

Developing Recommendations

Underpinning this section is the concept of the 'strength' of a recommendation. This takes into account the quality of the evidence but is conceptually different. Some recommendations are 'strong' in that the GDG believes that the vast majority of healthcare and other professionals and patients would choose a particular intervention if they considered the evidence in the same way that the GDG has. This is generally the case if the benefits clearly outweigh the harms for most people and the intervention is likely to be cost effective. However, there is often a closer balance between benefits and harms, and some patients would not choose an intervention whereas others would. This may happen, for example, if some patients are particularly averse to some side effect and others are not. In these circumstances the recommendation is generally weaker, although it may be possible to make stronger recommendations about specific groups of patients.

Over the course of the guideline development process, the GDG was presented with:

- Evidence tables of the clinical and economic evidence reviewed from the literature. All evidence tables are in Appendices H and I in the full version of the original guideline document.
- Summary of clinical and economic evidence and quality (as presented in Chapters 5-16 in the full version of the original guideline document).
- Forest plots and summary receiver operating characteristic (ROC) curves (Appendix I in the full version of the original guideline document).
- A description of the methods and results of the cost-effectiveness analysis undertaken for the guideline (Appendix L in the full version of the original guideline document).

Recommendations were drafted on the basis of the GDG interpretation of the available evidence, taking into account the balance of benefits, harms and costs between different courses of action. This was either done formally in an economic model, or informally. Firstly, the net benefit over harm (clinical effectiveness) was considered, focusing on the critical outcomes. When this was done informally, the GDG took into account the clinical

benefits and harms when one intervention was compared with another. The assessment of net benefit was moderated by the importance placed on the outcomes (the GDG's values and preferences), and the confidence the GDG had in the evidence (evidence quality). Secondly, it was assessed whether the net benefit justified any differences in costs.

When clinical and economic evidence was of poor quality, conflicting or absent, the GDG drafted recommendations based on their expert opinion. The considerations for making consensus-based recommendations include the balance between potential harms and benefits, the economic costs compared to the economic benefits, current practices, recommendations made in other relevant guidelines, patient preferences and equality issues. The consensus recommendations were agreed through discussions in the GDG. The GDG also considered whether the uncertainty was sufficient to justify delaying making a recommendation to await further research, taking into account the potential harm of failing to make a clear recommendation.

The wording of recommendations was agreed by the GDG and focused on the following factors:

- The actions health professionals need to take
- The information readers need to know
- The strength of the recommendation (for example the word 'offer' was used for strong recommendations and 'consider' for weak recommendations)
- The involvement of patients (and their carers if needed) in decisions on treatment and care
- Consistency with NICE's standard advice on recommendations about drugs, waiting times and ineffective interventions (see chapter 9.3, Creating guideline recommendations in the NICE Guidelines Manual [see the "Availability of Companion Documents" field]). The main considerations specific to each recommendation are outlined in the 'Recommendations and link to evidence' sections within each chapter.

Rating Scheme for the Strength of the Recommendations

Strength of Recommendations

Some recommendations can be made with more certainty than others. The Guideline Development Group (GDG) makes a recommendation based on the trade-off between the benefits and harms of an intervention, taking into account the quality of the underpinning evidence. For some interventions, the GDG is confident that, given the information it has looked at, most patients would choose the intervention. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the strength of the recommendation).

Interventions That Must (or Must Not) Be Used

The GDG usually uses 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally the GDG uses 'must' (or 'must not') if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

Interventions That Should (or Should Not) Be Used – a 'Strong' Recommendation

The GDG uses 'offer' (and similar words such as 'refer' or 'advise') when confident that, for the vast majority of patients, an intervention will do more good than harm, and be cost effective. Similar forms of words (for example, 'Do not offer…') are used when the GDG is confident that an intervention will not be of benefit for most patients.

Interventions That Could Be Used

The GDG uses 'consider' when confident that an intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.

Note: The National Institute for Health and Care Excellence (NICE) began using this approach to denote the strength of recommendations in guidelines that started development after publication of the 2009 version of 'The guidelines manual' (January 2009). This does not apply to any recommendations ending [2008]. In particular, for recommendations labelled [2008] the word 'consider' may not necessarily be used to denote the strength of the recommendation.

Cost Analysis

Relevant health economic evidence for recommendations can be found in the specific chapters of the full version of the original guideline document

(see the "Availability of Companion Documents" field).

See Appendix L in the full version of the original guideline document for details of the cost-effectiveness analysis for low-intensity, medium-intensity and high-intensity statin treatment for the primary and secondary prevention of cardiovascular disease (CVD).

Undertaking New Health Economic Analysis

As well as reviewing the published economic literature for each review question, as described above, new economic analysis was undertaken by the health economist in selected areas. Priority areas for new health economic analysis were agreed by the GDG after formation of the review questions and consideration of the available health economic evidence.

The GDG identified the cost-effectiveness of statin therapy as the highest priority area for original economic modelling, due to statins being the preferred first-line treatment, substantial changes in the costs of statins since the previous version of this guideline was published, and a lack of published evidence using current UK costs, leading to considerable uncertainty regarding which intensity of statin is preferable and the threshold of cardiovascular risk above which primary preventative treatment should be initiated.

The following general principles were adhered to in developing the cost-effectiveness analysis:

- Methods were consistent with the NICE reference case.
- The GDG was involved in the design of the model, selection of inputs and interpretation of the results.
- Model inputs were based on the systematic review of the clinical literature supplemented with other published data sources where possible.
- When published data was not available GDG expert opinion was used to populate the model.
- Model inputs and assumptions were reported fully and transparently.
- The results were subject to sensitivity analysis and limitations were discussed.
- The model was peer-reviewed by an external health economist.

Full methods for the cost-effectiveness analysis for statin therapy are described in Appendix L in the full version of the original guideline document.

Cost-effectiveness Criteria

The National Institute for Health and Care Excellence (NICE) report 'Social value judgements: principles for the development of NICE guidance' sets out the principles that Guideline Development Groups (GDGs) should consider when judging whether an intervention offers good value for money. In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

- The intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
- The intervention cost less than £20,000 per quality-adjusted life year (QALY) gained compared with the next best strategy.

If the GDG recommended an intervention that was estimated to cost more than £20,000 per QALY gained, or did not recommend one that was estimated to cost less than £20,000 per QALY gained, the reasons for this decision are discussed explicitly in the 'Recommendations and link to evidence' section of the relevant chapter, with reference to issues regarding the plausibility of the estimate or to the factors set out in 'Social value judgements: principles for the development of NICE guidance'.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

This guidance is subject to a 6-week public consultation and feedback as part of the quality assurance and peer review of the document. All comments received from registered stakeholders are responded to in turn and posted on the National Institute for Health and Care Excellence (NICE) website when the pre-publication check of the full guideline occurs.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate cardiovascular risk assessment and primary and secondary prevention of cardiovascular disease (CVD)

Refer to the "Trade off between clinical benefits and harms" sections in the full version of the original guideline document (see the "Availability of Companion Documents" field) for benefits of specific interventions.

Potential Harms

Statin therapy has been associated with the following adverse events: myalgia, myopathy, asthenia, creatine kinase elevation, elevated liver function tests, and rhabdomyolysis.

Refer to the "Trade off between clinical benefits and harms" sections in the full version of the original guideline document (see the "Availability of Companion Documents" field) for harms of specific interventions.

Contraindications

Contraindications

Statins are contraindicated in pregnancy and breastfeeding.

Qualifying Statements

Qualifying Statements

- This guidance represents the view of the National Institute for Health and Care Excellence (NICE), which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer and informed by the summary of product characteristics of any drugs they are considering.
- Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.
- The guideline will assume that prescribers will use a drug's summary of product characteristics to inform decisions made with individual patients.
- This guideline recommends some drugs for indications for which they do not have a UK marketing authorisation at the date of publication, if there is good evidence to support that use. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient (or those with authority to give consent on their behalf) should provide informed consent, which should be documented. See the General Medical Council's Good practice in prescribing and managing medicines and devices

for further information. Where recommendations have been made for the use of drugs outside their licensed indications ('off-label use'), these drugs are marked with a footnote in the recommendations.

- Patients and healthcare professionals in England have rights and responsibilities as set out in the National Health Service (NHS) Constitution for England – all NICE guidance is written to reflect these. Treatment and care should take into account individual needs and preferences. Patients should have the opportunity to make in for med decisions about their care and treatment, in partnership with their healthcare professionals. If someone does not have the capacity to make decisions, healthcare professionals should follow the Department of Health's advice on consent, the code of practice that accompanies the Mental Capacity Act and the supplementary code of practice on deprivation of liberty safeguards
- NICE has produced guidance on the components of good patient experience in adult NHS services. All healthcare professionals should follow the recommendations in Patient experience in adult NHS services.
- For all recommendations, NICE expects that there is discussion with the patient about the risks and benefits of the interventions, and their values and preferences. This discussion aims to help them to reach a fully informed decision.

Implementation of the Guideline

Description of Implementation Strategy

Implementation tools and resources to help put the guideline into practice are available.

Key Priorities for Implementation

The following recommendations have been identified as priorities for implementation.

Identifying and Assessing Cardiovascular Disease (CVD) Risk

- For the primary prevention of CVD in primary care, use a systematic strategy to identify people who are likely to be at high risk. [2008, amended 2014]
- Prioritise people for a full formal risk assessment if their estimated 10-year risk of CVD is 10% or more. [2008, amended 2014]
- Use the QRISK2 risk assessment tool to assess CVD risk for the primary prevention of CVD in people up to and including age 84 years. [new 2014]
- Do not use a risk assessment tool to assess CVD risk in people with an estimated glomerular filtration rate (eGFR) less than 60 ml/min/1.73 m^2 and/or albuminuria*. These people are at increased risk of CVD. See "People with CKD" in the "Major Recommendations" field for advice on treatment with statins for people with chronic kidney disease. [new 2014]

Lipid Modification Therapy for the Primary and Secondary Prevention of CVD

- Before starting lipid modification therapy for the primary prevention of CVD, take at least 1 lipid sample to measure a full lipid profile. This should include measurement of total cholesterol, high-density lipoprotein (HDL) cholesterol, non-HDL cholesterol, and triglyceride concentrations. A fasting sample is not needed. [new 2014]
- Offer atorvastatin 20 mg for the primary prevention of CVD to people who have a 10% or greater 10-year risk of developing CVD. Estimate the level of risk using the QRISK2 assessment tool. [new 2014]
- Start statin treatment in people with CVD with atorvastatin 80 mg†. Use a lower dose of atorvastatin if any of the following apply:
  - Potential drug interactions
  - High risk of adverse effects
  - Patient preference. [new 2014]
- Measure total cholesterol, HDL cholesterol and non-HDL cholesterol in all people who have been started on high-intensity statin treatment at 3 months of treatment and aim for a greater than 40% reduction in non-HDL cholesterol. If a greater than 40% reduction in non-HDL cholesterol is not achieved:
  - Discuss adherence and timing of dose
  - Optimise adherence to diet and lifestyle measures
  - Consider increasing dose if started on less than atorvastatin 80 mg and the person is judged to be at higher risk because of comorbidities, risk score or using clinical judgement. [new 2014]

This recommendation updates and replaces a recommendation from Type 1 diabetes: Diagnosis and management of type 1 diabetes in children,

young people, and adults (NICE clinical guideline 15).

*People on renal replacement therapy are outside the scope of this guideline.

†At the time of publication (July 2014), atorvastatin did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing and managing medicines and devices for further information.

Implementation Tools

Audit Criteria/Indicators

Clinical Algorithm

Patient Resources

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

National Clinical Guideline Centre. Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Jul. 50 p. (Clinical guideline; no. 181).

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

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Guideline Developer(s)

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Guideline Committee

Guideline Development Group

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Financial Disclosures/Conflicts of Interest

At the start of the guideline development process, all Guideline Development Group (GDG) members declared interests including consultancies, fee-paid work, share-holdings, fellowships and support from the healthcare industry. At all subsequent GDG meetings, members declared arising conflicts of interest. Members were either required to withdraw completely or for part of the discussion if their declared interest made it appropriate. The details of declared interests and the actions taken are shown in Appendix B in the full version of the original guideline document (see the "Availability of Companion Documents" field).

Guideline Status

This is the current release of the guideline.

This guideline updates previous versions:

National Collaborating Centre for Primary Care. Lipid modification. Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. London (UK): National Institute for Health and Clinical Excellence (NICE); 2008 May. 37 p. (Clinical guideline; no. 67).

National Institute for Health and Clinical Excellence (NICE). Statins for the prevention of cardiovascular events. London (UK): National Institute for Health and Clinical Excellence (NICE); 2006 Jan. 45 p. (Technology appraisal guidance; no. 94).

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site .

Availability of Companion Documents

The following are available:

- Lipid modification. Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. Full guideline. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Jul. 302 p. (Clinical guideline; no. 181). Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site .
- Lipid modification. Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. Appendices. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Jul. 829 p. (Clinical guideline; no. 181) Electronic copies: Available from the NICE Web site .
- Lipid modification. Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. Costing report. London (UK): National Institute for Health and Care Excellence; 2014 Jul. 27 p. (Clinical guideline; no. 181). Electronic copies: Available from the NICE Web site .
- Lipid modification. Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. Costing template. London (UK): National Institute for Health and Care Excellence; 2014 Jul. (Clinical guideline; no. 181). Electronic copies: Available from the NICE Web site .
- Lipid modification. Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. Clinical audit tool. London (UK): National Institute for Health and Care Excellence; 2014 Jul. (Clinical guideline; no. 181). Electronic copies: Available from the NICE Web site .
- The guidelines manual 2012. London (UK): National Institute for Health and Care Excellence (NICE); 2012 Nov. Electronic copies: Available from the NICE Web site .

Patient Resources

The following is available:

- Lowering cholesterol to reduce the risk of coronary heart disease and stroke. Information for the public. London (UK): National Institute for Health and Care Excellence; 2014 Jul. 12 p. (Clinical guideline; no. 181). Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site .

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NGC Status

This NGC summary was completed by ECRI on March 21, 2007. This summary was updated by ECRI Institute on June 27, 2011 following the U.S. Food and Drug Administration advisory on Zocor (simvastatin). This summary was updated by ECRI Institute on October 31, 2014. This summary was updated by ECRI Institute on April 8, 2015 following the U.S. Food and Drug Administration advisory on Chantix (varenicline).

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